

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 September 2002 (26.09.2002)

PCT

(10) International Publication Number
WO 02/074282 A1

- (51) International Patent Classification⁷: **A61K 9/10**,
A61P 29/00
- (21) International Application Number: PCT/SE02/00476
- (22) International Filing Date: 13 March 2002 (13.03.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0100901-8 15 March 2001 (15.03.2001) SE
- (71) Applicant (for all designated States except US): AS-
TRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): SIEKMANN, Britta
[DE/SE]; Camurus AB, Ideon Science Park, Sölvegatan 41,
S-223 70 Lund (SE). THORING, Barbro [SE/SE]; As-
traZeneca R & D Södertälje, S-151 85 Södertälje (SE).
- (74) Agents: ASTRAZENECA AB et al.; Global Intellectual
Property, S-151 85 Södertälje (SE).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
- (84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).
- Declarations under Rule 4.17:**
- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG,
UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS,
MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI,
CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only
- Published:**
- with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW COMPOSITION

(57) Abstract: A new pharmaceutical composition in the form of lipoglobules which comprises (a) one or more NO-releasing NSAID(s); (b) one or more surfactant(s); and (c) an aqueous phase, as well as a process for the preparation of such composition and the use of such composition in the treatment of pain and inflammation.

WO 02/074282 A1

NEW COMPOSITION

Field of the invention

The present invention is related to a new pharmaceutical composition in the form of lipoglobules which comprises (a) one or more NO-releasing NSAID; (b) one or more surface active agent(s); and (c) an aqueous phase, and to a process for the preparation of such composition. The claimed composition is intended for oral, topical, rectal, nasal and parenteral administration in humans and animals. The present invention also relates to the use of the new composition in the treatment of pain and inflammation.

Background and Prior Art

Nitrogen oxide releasing nonsteroidal antiinflammatory drugs (in the following named NO-releasing NSAIDs or shorter NO-NSAIDs) have recently been found to have an improved side-effect profile, see e.g. WO 94/04484, WO 94/12463, WO 95/09831 and WO95/30641, compared to the well-known drugs used in the treatment of pain and inflammation, NSAIDs. Patients undergoing treatment with NSAIDs for a longer period of time often experience problems with stomach gastrointestinal side-effects.

NO-NSAIDs are in general lipophilic compounds with poor aqueous solubility. NO-NSAIDs are practically insoluble in water. This inherent property of NO-NSAIDs poses a number of problems to the formulator. Upon oral administration, the absorption of NO-NSAIDs from the gastrointestinal tract (GIT) may be dissolution rate limited due to poor solubility in gastrointestinal fluids, which in turn results in poor bioavailability. For

parenteral, in particular intravenous administration, an aqueous based formulation is required which provides sufficient solubility of the NO-NSAID compound to reach therapeutic plasma levels.

- 5 Surfactants are known to be able to increase the solubility of poorly water soluble compounds. Different types of surfactant based drug delivery systems are known, such as micellar solutions, vesicular systems, e.g. liposomes, and emulsions.

Micellar solutions comprise the drug solubilised in a surfactant aggregate, e.g. spherical
10 micelles, in an aqueous medium. Typically, the diameter of these aggregates is in the order of two molecular lengths of the surfactant molecule, i.e. some ten to hundred Ångström.

According to the Gibbs phase law, micellar solutions represent one phase systems.

Disadvantages of micellar systems are that the solubility enhancement by the surfactant is usually only modest, or that high surfactant-to-drug ratios are required to obtain sufficient
15 solubility. A high surfactant load is not desirable from a toxicological point of view. Upon administration of micellar systems, there is a risk that the drug may precipitate when the micellar system is diluted in gastrointestinal fluids or in the blood. In oral administration, precipitation may lead to reduced bioavailability. In intravenous administration, drug precipitation may lead to pain upon injection, venal tissue irritation, and embolism.

20

Vesicles are bilayer systems in which an aqueous space is surrounded by one (unilamellar) or more (oligo- and multilamellar) surfactant bilayers. In liposomes these bilayers consist of phospholipids. Hydrophilic drugs can be incorporated in the internal aqueous phase whereas lipophilic drugs partition into the surfactant bilayer. Vesicle dispersions are two

phase systems. Typically, the vesicle diameter is in the nanometer to micrometer range depending on the number of bilayers. The amount of lipophilic drug that can be incorporated into the surfactant bilayers is usually low because the drug may disturb the bilayer structure leading to instability.

5

Emulsions represent dispersions of one liquid in another, not miscible liquid, typically by the aid of a surfactant acting as an emulsifier. Two basic types can be distinguished, oil-in-water (o/w) and water-in-oil (w/o). Oil-in-water emulsions comprise an aqueous continuous phase in which oil droplets are dispersed. In w/o emulsions an aqueous phase is dispersed in an oily continuous medium. For intravenous administration, only the o/w emulsions can be used, provided that the size of the oil droplets is small enough to prevent blockage of blood capillaries. Submicron sized o/w emulsions have been used in parenteral nutrition for a long time. Emulsions as delivery systems for poorly water soluble drugs comprise at least four components, (a) a drug, (b) a lipid phase, (c) an emulsifier, and (d) 10 an aqueous phase. The poorly water soluble drug is usually dissolved in the lipid phase. Thus, in this case the lipid phase is used to solubilise the drug whereas the surfactant serves as a dispersion aid and as a stabiliser of the oil phase. As with micellar and vesicular systems, the solubilisation capacity of o/w emulsions is generally low. It is determined by the solubility of the drug in the oil phase.

20

Outline of the invention

It has now surprisingly been found that the problems outlined above can be solved by a novel type of surfactant based delivery system for NO-NSAIDs, a pharmaceutical

5 composition in the form of lipoglobules.

The present invention discloses pharmaceutical compositions in the form of lipoglobules comprising the following components

- (a) one or more NO-releasing NSAID(s);
- 10 (b) one or more surfactant(s); and
- (c) an aqueous phase

wherein the NO-releasing NSAID(s) is a lipophilic core surrounded by one or more layers of surfactant(s), which NO-releasing NSAID(s) and surfactant(s) are dispersed in an aqueous phase.

15

Optionally the NO-NSAID compound(s) can be mixed with one or more lipophilic water-immiscible solvent(s), e.g. in order to adjust the density difference between the aqueous and the oil phase. The density of NO-NSAIDs is usually greater than that of water, and adjustment of densities may be advantageous to prevent sedimentation of the NO-NSAID
20 lipoglobules. Density adjustment can also be obtained by increasing the density of the aqueous phase, e.g. by adding sugars, sugar alcohols or salt.

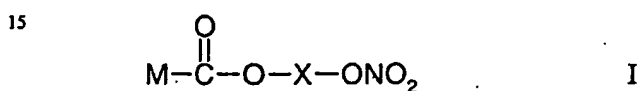
Depending on solubility, the surfactant(s) can be dissolved in either the aqueous or the lipophilic phase.

One of the unique features with NO-NSAIDs is that many of these lipophilic compounds are oils or thermosoftening semisolids which are practically insoluble in water. They can thus serve as the oil phase as such, of an o/w emulsion. These compounds can be

5 emulsified in an aqueous phase by a surfactant providing lipoglobules consisting of the NO-NSAID compound(s) as a core surrounded by one or more surfactant monolayers and dispersed in an aqueous medium. The surfactant layer stabilises the lipoglobules against aggregation and coalescence. Thermosoftening NO-NSAIDs may be heated above their melting point prior to emulsification to facilitate homogenisation, or may be dissolved in a

10 liquid NO-NSAID or in another lipophilic, water-immiscible solvent.

Preferred NO-releasing NSAIDs in accordance with the present invention, are compounds of the formula I

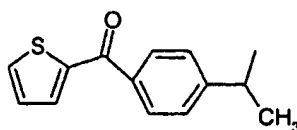
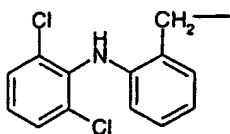


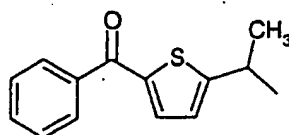
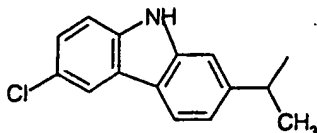
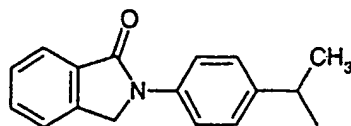
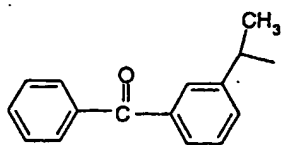
wherein

X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group

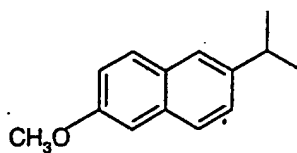
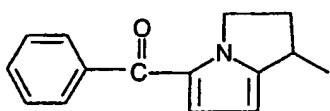
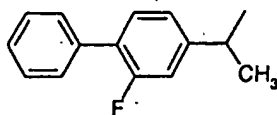
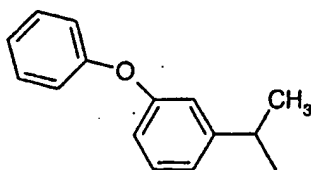
20 and the NSAID; and

M is selected from anyone of

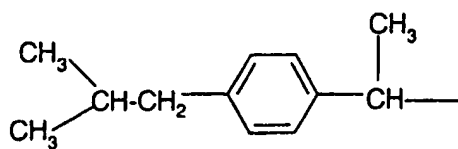
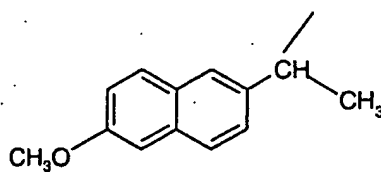
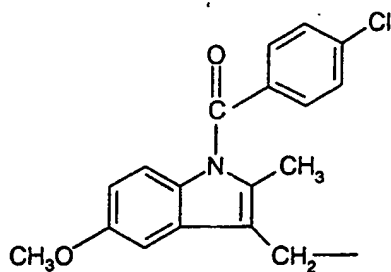




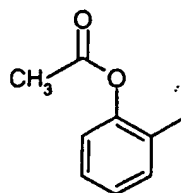
5



10



and



15

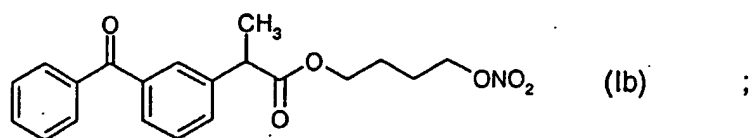
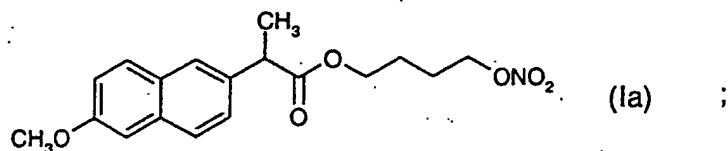
In a preferred embodiment of the invention, the spacer X is selected from a linear, branched or cyclic alkylene group $-(CH_2)_n$ wherein n is an integer of from

2 to 10; and $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$.

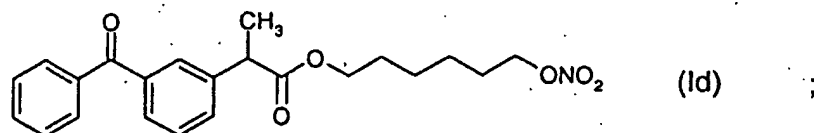
In one embodiment of the invention, NO-NSAIDs contemplated as active compounds in the compositions according to the present invention, are compounds disclosed and claimed in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641, which are hereby incorporated by reference.

Specific NO-releasing substances useful in accordance with the present invention are

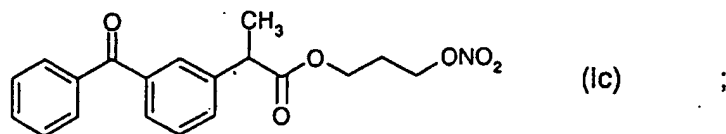
10



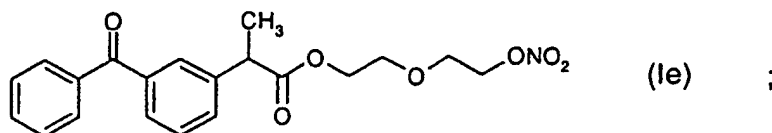
15



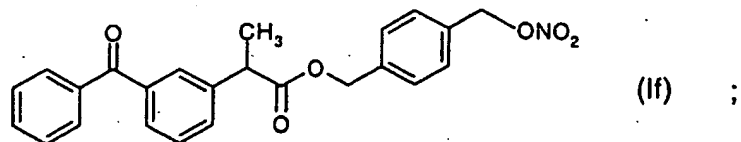
20



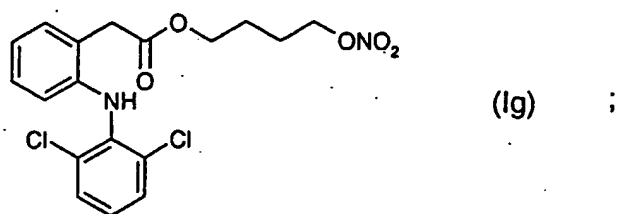
25



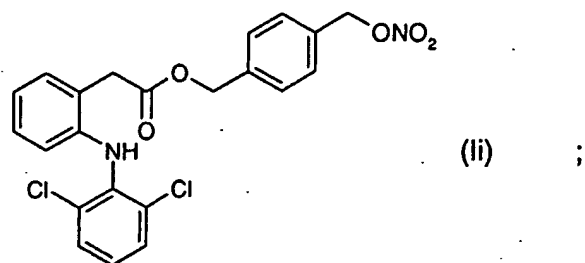
8



5

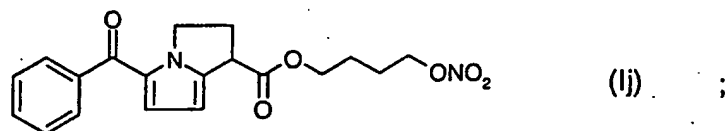


10

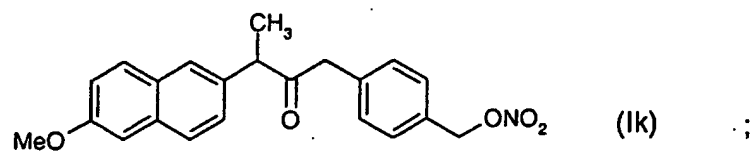


15

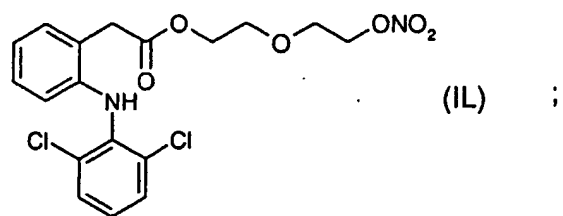
20



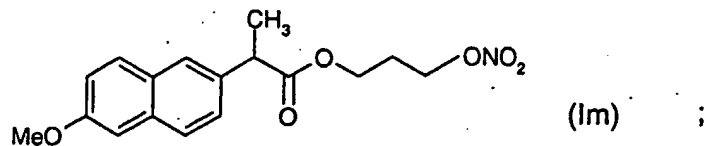
25



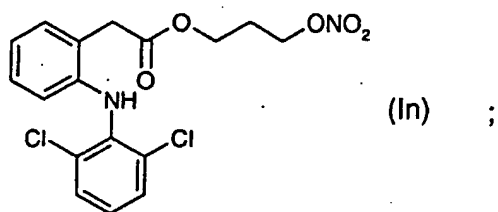
30



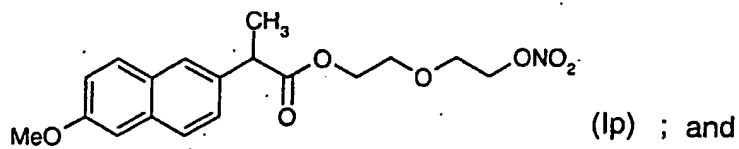
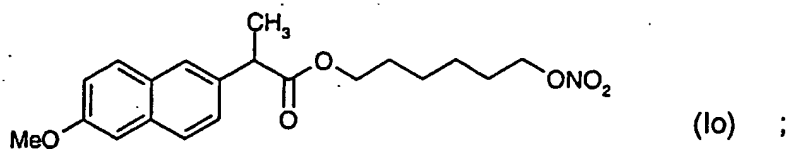
5



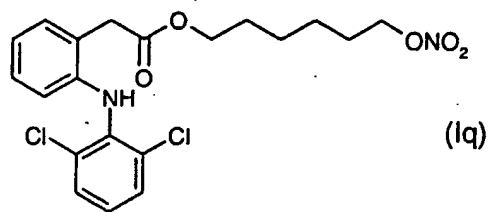
10



15



20



25

Most preferred NO-NSAIDs useful according to the invention are compounds of formulas Ia and Ig.

Suitable surfactants include, but are not limited to, phospholipids, e.g. naturally occurring phospholipids such as egg and soy lecithin; synthetic or semisynthetic phospholipids such as phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylinositols and phosphatidic acids; ethoxylated phospholipids such as polyoxyethylen-phosphatidylethanolamine; galactolipids and other glycolipids; bile acids such as cholic acid, taurocholic acid and glycocholic acid and their salts; sterols such as cholesterol, sitosterol, sitostanol and esters thereof; ethoxylated sterols such as polyoxyethylene sitosterol; fatty acids and their salts; mono- and diglyceride esters of fatty acids, e.g. monooleate and monostearate; fatty acid esters and alcohols; ethoxylated fatty acids, ethers and esters; ethoxylated castor oil, e.g. Cremophor EL; ethoxylated sorbitan esters such as polysorbates, e.g. polysorbate 80 (Tween 80); polypropylene-polyethylene block copolymers such as poloxamers, e.g. Poloxamer 188 and Poloxamer 407, and poloxamines, e.g. Tetronic 908; or a mixture of two or more of these surfactants.

Preferably the surfactant is one of a naturally occurring, synthetic or semi-synthetic phospholipid; a polypropylene polyethylene block copolymer; an ethoxylated sorbitan ester; or a mixture of two or more of these surfactants.

More preferred the surfactants is a naturally occurring phospholipid from soya in combination with a poloxamer, preferably poloxamer 407; or polysorbate 80.

A wide range of lipophilic, water-immiscible solvents can be used in the compositions of the present invention. Typically the water-immiscible solvent is a vegetable oil, e.g. soy bean, arachis, castor, corn, cottonseed, olive, safflower or sunflower oil. Suitable solvents

also include fractionated oils such as fractionated coconut oil. The water-immiscible solvent may also be a marine oil such as cod liver oil or other fish oils, also known as omega-3 polyunsaturated oils. Alternatively, the water-immiscible solvent is an ester of a medium or long-chain fatty acid, for example a mono-, di-, or triglyceride; or is a

5 chemically modified or manufactured material such as ethyl oleate, isopropyl myristate, isopropyl palmitate, a glycerol ester or polyoxyl hydrogenated castor oil. The compositions of the present invention may comprise a mixture of NO-NSAID and one or more of the above water-immiscible solvents.

10 The aqueous phase comprises water and may – depending on the intended way of administration - optionally contain buffering agents and salts; pH adjusting agents such as sodium hydroxide and hydrochloric acid; tonicity modifiers such as glycerol, xylitol, sorbitol, mannitol, and glucose; water-miscible solvents such as glycerol, ethanol, polyethylene glycol and propylene glycol; density modifiers such as polyols, sugars, sugar

15 alcohols and salts; viscosity modifiers such as thickeners and gelling agents; preservatives such as chlorhexidine, methyl-, ethyl-, propyl- or butylparaben, and thimerosal; antioxidants such as ascorbic acid and tocopherol derivatives; taste modifiers such as sugars, sweeteners and flavouring agents.

20 A composition of the present invention typically comprises one or more NO-NSAID(s) or mixtures of one or more NO-NSAID(s) and one or more water-immiscible solvent(s) in an amount that is up to 30% by weight of the composition, preferably 0.5-20%. The surfactant or surfactant mixture may be present in an amount up to 20% by weight of the composition, preferably 0.1-10%.

The dispersion techniques used in preparation of the present lipoglobule formulations can be conventional dispersion techniques such as high shear stirring, ultraturrax vortexing, sonication, high pressure homogenisation and microfluidisation. Preferably high pressure homogenisation or microfluidisation are used. The globule size is a function of the composition and dispersion parameters. As a general rule, globule size decreases with increasing amount of surfactant or with decreasing amount of the oil phase. Globule size also decreases with increasing energy input during dispersion until it levels off. Further energy input may lead to an increase in globule size, an effect known as overemulsification.

The globule size of the present lipoglobules is typically in the nanometer and micrometer range, more specifically from 50 nm to 50 μm , preferably 200 nm to 5 μm . Control of globule size is of importance for parenteral, in particular intravenous formulations. For intravenous administration, the average globule size should be below 1 μm , preferably 200-500 nm, with basically no globules above 5 μm present.

The pharmaceutical compositions in form of lipoglobules according to the present invention are suitable for oral, parenteral, topical, nasal and rectal administration of NO-NSAIDs. Where a formulation is to be used for parenteral administration, it must be sterile. Sterilisation is preferably performed by autoclavation. Ingredients in formulations for parenteral administration will have to be of injection grade and approved for such administration. Topical formulations should preferably be viscous and spreadable unless they are included in a patch.

The total amount of NO-NSAIDs used in the compositions of the invention is preferably in the range of 50-1500 mg per unit dose. In still a further preferred embodiment the amount of NO-NSAIDs used in the composition is 125-500 mg per unit dose.

- 5 The pharmaceutical lipoglobule composition of the present invention is particularly useful in the treatment of pain and inflammation. The wording "pain" is intended to include, but not limited to, nociceptive and neuropathic pain or combinations thereof; acute, intermittent and chronic pain; cancer pain; migraine and headaches of similar origin. The wording "inflammation" is intended to include, but not limited to, rheumatoid arthritis; 10 osteoarthritis; and juvenile arthritis.

Methods of preparation

The compositions according to present invention may be prepared according to one of the 15 following processes wherein

- i) one or more surfactant(s) is added to the aqueous phase whereupon one or more NO-NSAID(s) is dispersed in the aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation; or
- ii) one or more NO-NSAID(s) is mixed with one or more surfactant(s), whereupon the 20 mixture is dispersed in the aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation; or
- iii) one or more surfactant(s) is added to the aqueous phase and one or more NO-NSAID(s) is mixed with one or more lipophilic water-immiscible solvent(s), whereupon the mixture of NO-NSAID(s) and lipophilic immiscible solvent(s) is dispersed in the

aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation;

iv) one or more NO-NSAID(s) is mixed with one or more surfactant(s) and one or more lipophilic water-immiscible solvent(s), whereupon the mixture is dispersed in the aqueous

5 phase phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation;

v) one or more surfactant(s) is added to the aqueous phase, and one or more surfactant(s) is mixed with one or more NO-NSAID(s), whereupon the mixture of NO-NSAID(s) and surfactant(s) is dispersed in the aqueous phase by using conventional dispersion techniques

10 such as high shear mixing, sonication or high pressure homogenisation; or

vi) one or more surfactant(s) is added to the aqueous phase, and one or more surfactant(s)

as

well as one or more lipophilic water-immiscible solvent(s) is mixed with one or more NO-NSAID(s) whereupon the mixture of NO-NSAID(s), surfactant(s) and lipophilic water-

15 immiscible solvent(s) is dispersed in the aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation.

Thermosoftening NO-NSAIDs may be heated above their melting point prior to emulsification to facilitate homogenisation, or may be dissolved in a liquid NO-NSAID or
20 in another lipophilic, water-immiscible solvent.

Detailed description of the invention

The invention will now be described in more detail by the following examples, which are
5 not to be construed as limiting the invention.

Example 1

Composition	Ex. 1.1	Ex. 1.2	Ex. 1.3	Ex. 1.4	Ex. 1.5
	mg/g	mg/g	mg/g	mg/g	mg/g
Compound of formula Ia	0.77	1.30	1.06	1.06	21.2
Fractionated coconut oil	2.97	4.90	4.00	100.1	79.9
Phospholipon 80	0.76	1.32	1.08	21.6	21.6
Poloxamer 407	1.61	2.81	2.30	45.9	45.9
Water	To 1000	To 1000	To 1000	To 1000	To 1000

10

Preparation:

1. Aqueous phase: Fractionated soya phospholipid (Phospholipon 80) and poloxamer 407 (Lutrol F127) were dispersed in water with an Ultra Sonic rod or a high shear mixer.
- 15 2. Oil phase: Compound of formula Ia and coconut oil were mixed by hand stirring during heating to maximum 60°C.
3. The aqueous phase and oil phase were poured together. Emulsion was formed by sonication with an ultra sonic rod, or by first mixing with a high shear mixer and then homogenising with a high pressure homogeniser, until average droplet size is < 300 nm (as
20 measured by photon correlation spectroscopy in a Malvern PCS 4700).

Optionally the emulsion was autoclaved (15 min at 121°C) to prevent microbiological growth, and then stored at room temperature for at least 6 months.

The oral bioavailability of compound of formula Ia in lipoglobules of example 1.1, measured as the relative bioavailability of its metabolite naproxen (analysed naproxen-plasma level relative to given dose of compound of formula Ia), was 88 % in rat (4 ml/kg).

Example 2

10

Composition	Ex. 2.1	Ex. 2.2
	mg/g	mg/ml
Compound of formula Ia	0.87	1.30
Fractionated coconut oil	3.28	4.87
Polysorbate 80	1.38	2.06
Sodium-Carboxy methyl cellulose, medium viscous	14.6	14.9
Water	To 1000	To 1000

Preparation:

1. Oil phase: Compound of formula Ia and coconut oil were mixed by hand stirring during heating to maximum 60°C.
2. Polysorbate was added to the oil phase whereafter the mixture was heated to 60 °C and stirred for 1 minute with a high shear mixer.
3. Water heated to 60 °C was added in small portions while stirring with high shear mixer. In total the amount of water was approximately twice the amount of oil phase in step 1.
4. The mixture was stirred with high shear mixer for 2 minutes at 60 °C.
5. Stirring with high shear mixer for 2 minutes while cooling to room temperature.

6. Water was added in an amount enough to double the amount of emulsion whereafter the mixture was mixed until homogeneous.

7. Sodium-carboxymethylcellulose suspension, mediumviscous, 1,5 % in water was added. Stirring with magnet for 10 minutes.

Mean droplet size is $< 2 \mu\text{m}$, 90 % of the droplets are $< 5 \mu\text{m}$ (as measured by laser diffraction in a Coulter LS230).

The oral bioavailability of compound of formula Ia in example 2.1, measured as the relative bioavailability of its metabolite naproxen (analysed naproxen-plasma level relative to given dose of compound of formula Ia), was 95 % in rat (4 ml/kg).

Example 3

Composition	Ex. 3:1
	mg/g
Compound of formula Ia	187.5
Polysorbate 80	62.5
Water	750.0

Preparation:

1. Oil phase: Compound of formula Ia and Polysorbate were mixed with high shear mixer at temperature maximum 60°C.

2. Water heated to 60 °C was added in small portions while stirring with high shear mixer. In total the amount of water was approximately twice the amount of oil phase in step 1.

3. Stirring with high shear mixer for 2 minutes at 60 °C.

4. Stirring with high shear mixer for 2 minutes while cooling to room temperature.

5. The rest of the water was added and mixed with magnet until homogeneous.

Mean droplet size is $< 2 \mu\text{m}$, 90 % of the droplets are $< 5 \mu\text{m}$ (measured with LS).

5 **Example 4**

Composition	Ex. 4.1
	mg/g
Compound of formula Ig	0.25
Fractionated coconut oil	0.94
Phospholipon 80	0.25
Poloxamer 407	0.54
Water	To 1000

Preparation:

- 10 1. Aqueous phase: Fractionated soya phospholipid (Phospholipon 80) and poloxamer 407 (Lutrol F127) were dispersed in water with suitable mixing equipment.
2. Oil phase: Compound of formula Ig and coconut oil were mixed during gentle stirring.
3. The aqueous phase was slowly added to the oil phase during stirring. The emulsion was homogenised, e.g. with an ultra sonic rod or homogeniser, to eliminate the risk of large
- 15 droplets.

90% or more of the droplets formed have a particle size smaller than $0.2 \mu\text{m}$.

Example 5

20

Composition	Ex. 5.1
	mg/g
Compound of formula Ig	0.413

Fractionated coconut oil	99.6
Poloxamer 407	19.8
Water	To 1000

Composition	Ex. 5.2
	mg/g
Compound of formula IL	0.429
Fractionated coconut oil	100
Poloxamer 407	19.8
Water	To 1000

Composition	Ex. 5.3
	mg/g
Compound of formula Ic	0.357
Fractionated coconut oil	99.6
Poloxamer 407	19.8
Water	To 1000

Composition	Ex. 5.4
	mg/g
Compound of formula If	0.419
Fractionated coconut oil	99.6
Poloxamer 407	19.8
Water	To 1000

5 Preparation:

1. Oil-phase: The NO-releasing compound of formula Ig, IL, Ic and If, respectively, was mixed with the coconut oil by stirring. Heating to max 40°C was used if needed.

2. Aqueous phase: The poloxamer 407 was dispersed in the water by high-shear mixer.

3. The aqueous phase and the oil phase were mixed together. Emulsion was formed by first mixing with a high shear mixer and then homogenising with a high-pressure homogeniser.

- 5 Mean droplet size was 0.13-0.15 μm , 99 % of the droplets were < 0.23-0.25 μm (as measured by laser diffraction in a Coulter LS230).

The oral bioavailability of compound of formula Ig and compound of formula IL in lipoglobules, expressed as the systemic exposure to diclofenac (their active metabolite)
10 relative to the systemic exposure following intravenous administration of diclofenac, was 85 % and 104 % respectively in the minipig (5 ml/kg).

The oral bioavailability of compound of formula Ic and compound of formula If in lipoglobules, expressed as the systemic exposure to ketoprofen (their active metabolite)
15 relative to the systemic exposure following intravenous administration of ketoprofen, was 82 % and 80 % respectively in the minipig (5 ml/kg)

Example 6

Composition	Ex. 6.1
	mg/g
Compound of formula Ia	20.8
³ H-labelled Compound of formula Ia	7×10^{-8}
Poloxamer 407	4.16
Water	To 1000

Preparation:

1. Aqueous phase: Poloxamer 407 was dissolved in cold water over night.
2. Oil phase: Compound of formula Ia and 3H-labelled compound of formula Ia dissolved
5 in ethanol were mixed by adding more ethanol. The ethanol was then evaporated.
3. The aqueous phase and the oil phase were mixed together. Emulsion was formed by sonication with an ultra sonic rod.

At in-vitro permeation studies with human skin a steady state flux between 0,20-0,72
10 $\mu\text{g}/\text{cm}^2/\text{h}$ was achieved.

Example 7

Composition	Ex. 7.1
	mg/g
Compound of formula Ia	20.8
Fractionated coconut oil	78.2
Poloxamer 407	19.8
Water	To 1000

Preparation:

1. Oil-phase: The NO-releasing compound was mixed with the coconut oil by stirring. Heating to max 60°C was used. The poloxamer 407 was dissolved in the oil-mixture during heating to max 60°C.
- 20 2. The water and the oil phase was poured together. Emulsion was formed by first mixing with a high shear mixer and then homogenising with a high-pressure homogeniser.

Optionally the emulsion was heat-treated (≤ 15 min at 121 °C) to prevent microbiological growth.

Mean droplet size was $< 0.5 \mu\text{m}$, 99 % of the droplets were $< 2 \mu\text{m}$ (as measured by laser diffraction in a Coulter LS230).

Claims

1. A pharmaceutical composition in form of lipoglobules comprising

(a) one or more NO-releasing NSAID(s);

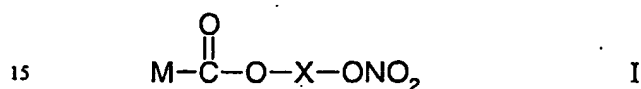
5 (b) one or more surfactant(s); and

(c) an aqueous phase

wherein the NO-releasing NSAID(s) is a lipophilic core surrounded by one or more layers of surfactant(s), which NO-releasing NSAID(s) and surfactant(s) are dispersed in an aqueous phase.

10

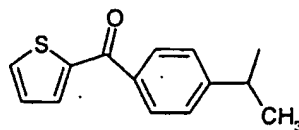
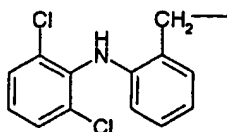
2. A pharmaceutical composition according to claim 1 wherein the NO-releasing NSAID is a compound of the formula I

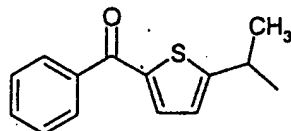
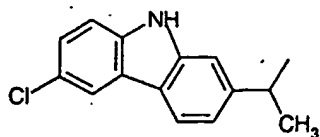
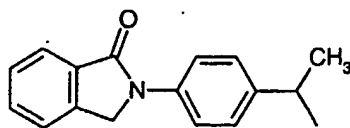
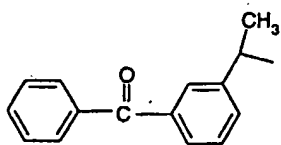


wherein

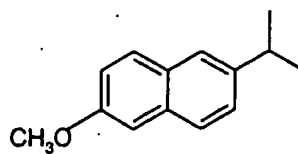
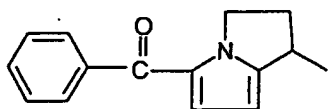
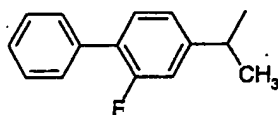
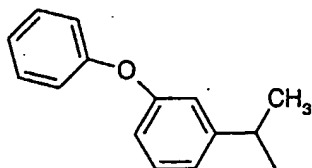
X is a spacer, and

20 M is selected from anyone of

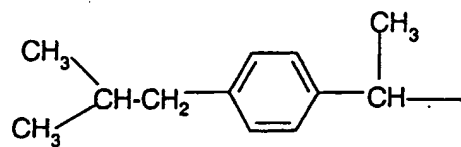
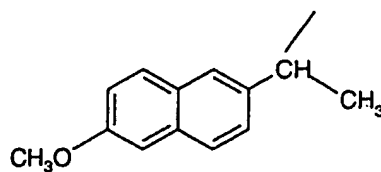
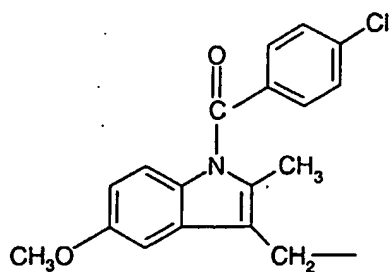




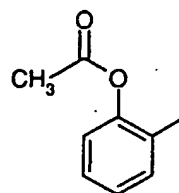
5



10



and

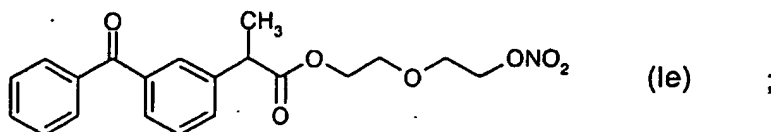
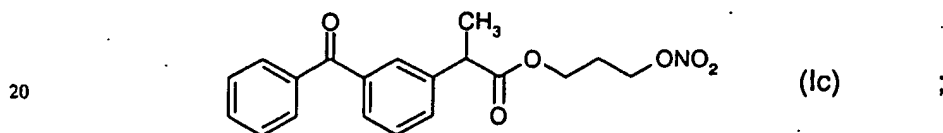
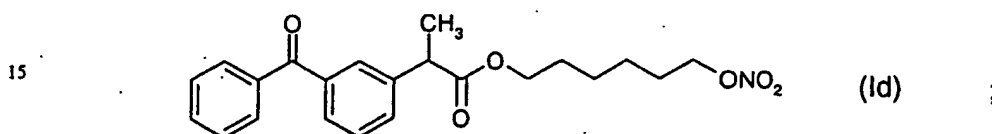
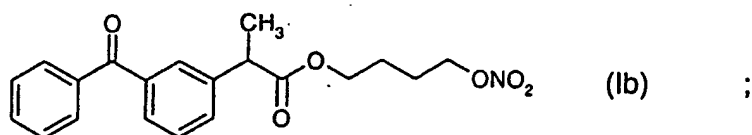
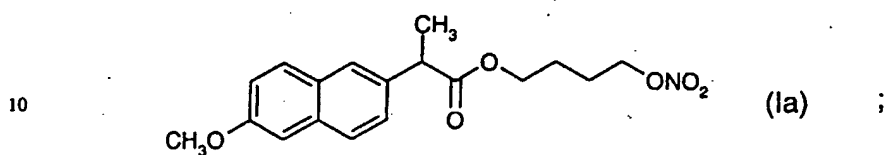


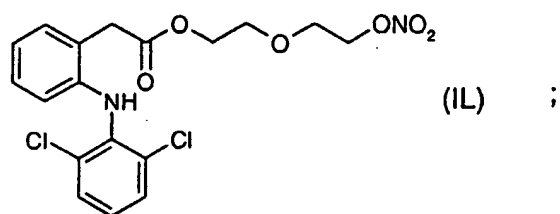
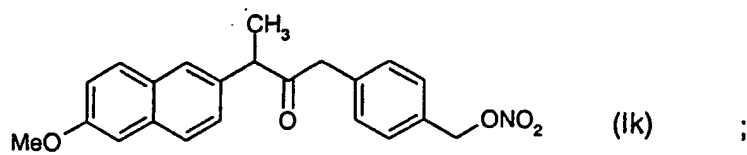
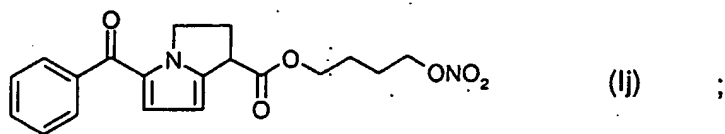
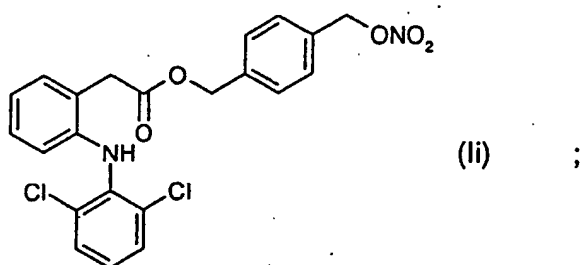
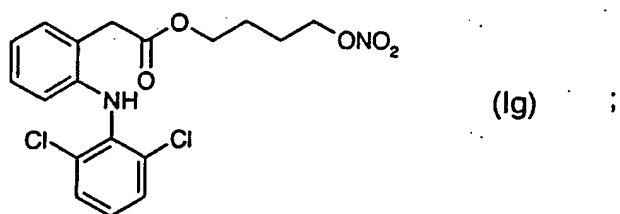
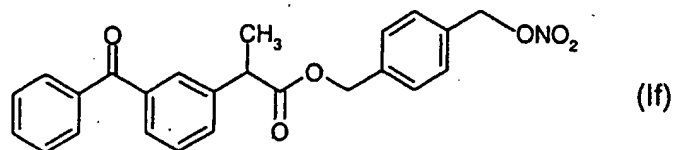
15

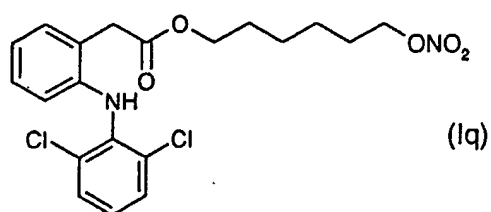
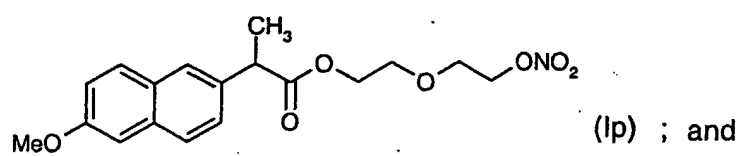
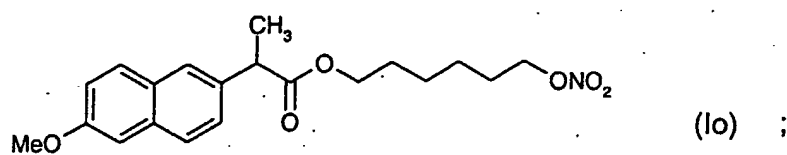
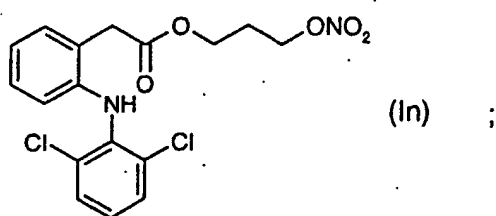
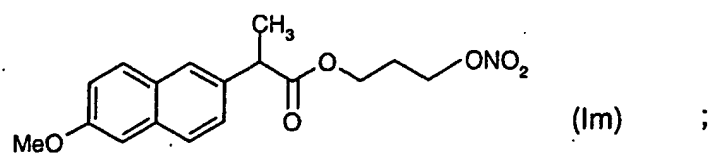
3. A pharmaceutical composition according to claim 2, wherein the spacer X of the NO-releasing NSAID is selected from a linear, branched or cyclic alkylene group $-(CH_2)_n$ wherein n is an integer of from 2 to 10; $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$.

5.

4. A pharmaceutical composition according to any one of the preceding claims, wherein the NO-releasing NSAID is any one compound selected from







5. A pharmaceutical composition according to claim 4 wherein the NO-releasing NSAID is a compound according to formula Ia.

6. A pharmaceutical composition according to claim 4 wherein the NO-releasing NSAID is a compound according to formula Ic, If, Ig or IL.
7. A pharmaceutical composition according to any one of the preceeding claims
5 wherein the surfactant is selected from phospholipids, e.g. naturally occurring phospholipids; synthetic or semisynthetic phospholipids; ethoxylated phospholipids; galactolipids and other glycolipids; bile acids and their salts; sterols and esters thereof; ethoxylated sterols; fatty acids and their salts; mono- and diglyceride esters of fatty acids; fatty acid esters and alcohols; ethoxylated fatty acids, ethers and
10 esters; ethoxylated castor oil; ethoxylated sorbitan esters; polypropylene-polyethylene block copolymers such as poloxamers and poloxamines; or mixtures of two or more of these surfactants.
8. A pharmaceutical composition according to claim 7 wherein the surfactant is one of
15 a naturally occurring, synthetic or semi-synthetic phospholipid; a polypropylene polyethylene block copolymer; an ethoxylated sorbitan ester; or a mixture of two or more of these surfactants.
9. A pharmaceutical composition according to claim 7 wherein the surfactant is a
20 naturally occurring phospholipid from soya in combination with a poloxamer.
10. A pharmaceutical formulation according to claim 7 wherein the surfactant is polysorbate 80.

11. A pharmaceutical composition according to any one of claims 1-10 wherein the NO-releasing NSAID lipophilic core further comprises one or more lipophilic water-immiscible solvent(s).
- 5 12. A pharmaceutical composition according to claim 11 wherein the lipophilic water-immiscible solvent is a vegetable oil; a fractionated oil; a marine oil; an ester of a medium or long-chain fatty acid; a chemically modified or manufactured material; or a mixture of two or more of the above water-immiscible solvents.
- 10 13. A pharmaceutical composition according to claim 11 wherein the lipophilic, water-immiscible solvent is fractionated coconut oil.
14. A pharmaceutical composition according to any one of the preceeding claims wherein the aqueous phase contains water and one or more of buffering agents; salts; pH
15 adjusting agents; tonicity modifiers; water miscible solvents; density modifiers; viscosity modifiers agents; preservatives; antioxidants; and taste modifiers.
15. A pharmaceutical composition according any one of the preceeding claims wherein the amount of NO-releasing NSAID or mixtures of NO-releasing NSAID and water-
20 immiscible solvent is up to 30% by weight of the composition.
16. A pharmaceutical composition according to claim 15 wherein the amount of NO-releasing NSAID or mixtures of NO-releasing NSAID and water-immiscible solvent is 0.5 – 20% by weight of the composition.

17. A pharmaceutical composition according to any one of the preceeding claims wherein the amount of surfactant is up to 20 % by weight of the composition.

5 18. A pharmaceutical composition according to claim 17 wherein the amount of surfactant is 0.1 – 10 % by weight of the composition.

19. A pharmaceutical composition according to any one of the preceeding claims for oral, rectal, parenteral, nasal or topical administration to a human or an animal.

10

20. Use of a pharmaceutical composition according to claims 1-18 for use in therapy.

21. Use according to claim 20 in the treatment of pain.

15

22. Use according to claim 20 in the treatment of inflammation.

23. A method for the treatment of pain which method comprises treating a subject suffering from said condition with a pharmaceutical composition according to any one of
20 claims 1-18.

24. A method for the treatment of inflammation which method comprises treating a subject suffering from said condition with a pharmaceutical composition according to any one of claims 1-18.

25. A process for the preparation of a composition according to any one of claims 1-20 wherein

- i) one or more surfactant(s) is added to an aqueous phase whereupon one or more NO-NSAID(s) is dispersed in the aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation; or
- ii) one or more NO-NSAID(s) is mixed with one or more surfactant(s), whereupon the mixture is dispersed in an aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation; or
- iii) one or more surfactant(s) is added to an aqueous phase and one or more NO-NSAID(s) is mixed with one or more lipophilic water-immiscible solvent(s), whereupon the mixture of NO-NSAID(s) and lipophilic water-immiscible solvent(s) is dispersed in the aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation; or
- iv) one or more NO-NSAID(s) is mixed with one or more surfactant(s) and one or more lipophilic water-immiscible solvent(s), whereupon the mixture is dispersed in an aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation; or
- v) one or more surfactant(s) is added to the aqueous phase, and one or more surfactant(s) is mixed with one or more NO-NSAID(s), whereupon the mixture of NO-NSAID(s) and surfactant(s) is dispersed in the aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation; or
- vi) one or more surfactant(s) is added to the aqueous phase, and one or more surfactant(s) as well as one or more lipophilic water-immiscible solvent(s) is mixed with one or more NO-NSAID(s), whereupon the mixture of NO-NSAID(s), surfactant(s) and lipophilic

water-immiscible solvent(s) is dispersed in the aqueous phase by using conventional dispersion techniques such as high shear mixing, sonication or high pressure homogenisation.

- 5 26. A process according to claim 25 wherein the NO-releasing NSAID(s) is heated above its melting point prior to dispersion in the aqueous phase.

10

15

20

25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00476

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/10, A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4622219 A (DUNCAN H. HAYNES), 11 November 1986 (11.11.86) --	1-26
X	US 4882164 A (ALBERTO FERRO ET AL), 21 November 1989 (21.11.89) --	1-26
X	WO 9932089 A1 (ASTRA AKTIEBOLAG), 1 July 1999 (01.07.99) --	1-26
A	EP 0274870 A2 (T.I.L. MEDICAL LTD.), 20 July 1988 (20.07.88) -- -----	1-26

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

13 June 2002

Date of mailing of the international search report

26 -06- 2002

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Viveca Norén/EÖ
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00476

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20-24
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet*
2. ☒ Claims Nos.: 1
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet**
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int. application No.
PCT/SE02/00476

*

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

**

The expression "NO-releasing NSAID(s)" covers a large number of compounds with different properties and industrial applicability for all of the claimed invention has not been demonstrated. A complete search of the claimed scope is impossible to perform. Hence a search has been performed as far as possible on the general expression but has mainly been focused on compositions comprising the compounds defined in claim 2.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00476

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
US	4622219	A	11/11/86	AT	60708 T	15/02/91
				CA	1242645 A	04/10/88
				DE	3484104 D	00/00/00
				EP	0153926 A,B	11/09/85
				SE	0153926 T3	
				JP	2518605 B	24/07/96
				JP	60501557 T	19/09/85
				US	4725442 A	16/02/88
				WO	8500011 A	03/01/85
US	4882164	A	21/11/89	AT	71288 T	15/01/92
				AU	599198 B	12/07/90
				AU	1076688 A	04/08/88
				CA	1319886 A	06/07/93
				DE	3867502 A	20/02/92
				DK	4088 A	04/08/88
				EP	0280887 A,B	07/09/88
				SE	0280887 T3	
				ES	2040278 T	16/10/93
				IE	61068 B	21/09/94
				JP	2645427 B	25/08/97
				JP	63201133 A	19/08/88
				NZ	223290 A	27/11/90
				PH	24848 A	26/12/90
				ZA	8800562 A	03/08/88
WO	9932089	A1	01/07/99	AU	1993599 A	12/07/99
				BR	9813811 A	03/10/00
				CA	2315782 A	01/07/99
				CN	1283106 T	07/02/01
				EE	200000388 A	15/02/02
				EP	1043973 A	18/10/00
				HU	0102365 A	28/11/01
				JP	2001526210 T	18/12/01
				NO	20003220 A	22/08/00
				PL	341361 A	09/04/01
				SE	9704833 D	00/00/00
				SK	9532000 A	07/11/00
				TR	200001977 T	00/00/00
				ZA	9811461 A	22/06/99
EP	0274870	A2	20/07/88	AU	605812 B	24/01/91
				AU	8263987 A	23/06/88
				DK	664387 A	19/06/88
				GB	8630273 D	00/00/00
				IE	342787 L	18/06/88
				IE	873427 L	18/06/88
				JP	63277617 A	15/11/88
				NZ	222955 A	26/10/90
				US	4944949 A	31/07/90
				ZA	8709579 A	30/08/89